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1,3-Thiazino[6,5-*b*]indol-4-one derivatives. The first synthesis of indole phytoalexin cyclobrassinon

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Abstract—The first synthesis of indole phytoalexin cyclobrassinon in six steps, in 12% overall yield and some of its analogues, possessing a 1,3-thiazino[6,5-*b*]indol-4-one tricyclic ring system was performed, starting from 2-chloroindole-3-carboxaldehyde and employing the intramolecular Et_3N-mediated nucleophilic substitution of a chlorine atom in the 2-position of an indole ring with sulfur as a key step.

Phytoalexins are low molecular weight secondary metabolites, produced by plants after their exposure to physical, biological or chemical stress.[1] A specific group of these natural products represent indole phytoalexins produced by economically important plants of the family *Cruciferae* and cultivated worldwide.[2,3] With respect to the well known anticarcinogenic properties of brassica vegetables[4] it is quite important to study the biological activity of indole phytoalexins. Isolation from plants is difficult and time consuming and therefore the amounts required for screening should be provided by synthesis. Approximately 30 hitherto known indole phytoalexins have been synthesized[3] and biological screening disclosed antifungal,[5] cancerprotective[6,7] and antitumor[8,9] activity of several compounds. The synthesis and biological properties of cyclobrassinon (**6a**), isolated in 1994 from kohlrabi,[10] have not been described to date.

In continuation of our interest in the synthesis of indole phytoalexins,[11,12] we have decided to study the synthesis of cyclobrassinon, possessing the structurally unique 1,3-thiazino[6,5-*b*]indol-4-one ring system. To the best of our knowledge, there are only several examples of analogous compounds. One of them is another indole phytoalexin cyclobrassinin (2-methylsulfanyl-4*H*-1,3-thiazino[6,5-*b*]indole),[13] and two related compounds.[3,14] Cyclobrassinin was prepared by cyclization of phytoalexin brassinin [*N*-(indol-3-ylmethyl)dithiocarbamate] with pyridinium bromide perbromide,[13,15] or *N*-bromosuccinimide.[7] The other example is an unstable-2-imino-2*H*-1,3-thiazino[6,5-*b*]indole hydrochloride, obtained by heating of 2-chloroindole-3-carboxaldehyde with thiourea.[16]

To achieve the synthesis of **6a**, it was decided to use 2-chloroindole-3-carboxaldehyde (**1**)[16] as a starting material. Its transformation to monothiocarbamate of the type **4** via the corresponding acid, acid halide and isothiocyanate, and subsequent cyclization should afford the desired cyclobrassinon (**6a**). The preparation of the required 2-chloroindole-3-carboxylic acid was accomplished by oxidation of aldehyde **1** with $KMnO_4$ in aqueous acetone in the presence of a phosphate buffer[17] or $NaClO_2$ in aqueous dioxane in the presence of 2-methyl-but-2-ene.[18] However, oxidation of **1** in our hands did not afford 2-chloroindole-3-carboxylic acid in a reasonable yield. The same situation occurred with protected aldehyde **2**. Therefore, we turned our attention to the radical bromination of aldehydes (NBS, AIBN, CCl_4, reflux) to form substituted benzoyl bromides and aliphatic acid bromides.[19] However, under these conditions, aldehyde **1** completely decomposed. The problem was solved by introduction of the *t*-butoxycarbonyl (Boc) protecting group. Reaction of 1-Boc-2-chloroindole-3-carboxaldehyde (**2**) under the conditions of radical bromination gave the corresponding unstable acid bromide, which after treatment with KSCN afforded surprisingly stable-1-Boc-2-chloroindole-3-ylcarbonylisothiocyanate (**3**, Scheme 1).

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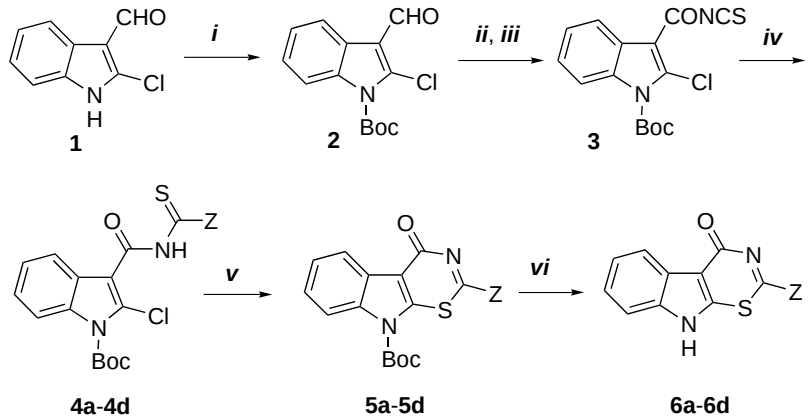

Scheme 1. For **4–6** Z = OCH_3 (**a**), OC_2H_5 (**b**), $NHCH_3$ (**c**), $N(CH_2)_5$ (**d**). *Reagents and conditions*: (**i**) Boc_2O, DMAP, THF, 5°C, 1 h, 68%; (**ii**) NBS, AIBN, tetrachloromethane, reflux, 10 min; (**iii**) KSCN, acetone, rt, 15 min, 41% (based on aldehyde **2**); (**iv**) **a**: CH_3OH, acetone, rt, 2 h, **b**: C_2H_5OH, acetone, rt, 2.5 h, **c**: CH_3NH_2, acetone, 0°C, 10 min, 44%, **d**: piperidine, acetone, 0°C, 5 min; (**v**) **a**: Et_3N, rt, 1 h, 61%, **b**: Et_3N, rt, 1.5 h, 64%, **c**: Et_3N, acetone, reflux, 3 h, 70%, **d**: Et_3N, acetone, rt, 2 h, 67% (for **5a**, **5b** and **5d** yields are based on isothiocyanate **3**); (**vi**) **a**: 165–170°C, 40 min, 70%, **b**: 165–170°C, 30 min, 80%, **c**: 180–185°C, 20 min, 72%, **d**: 155–160°C, 25 min, 77%.

Nucleophilic addition of methanol to isothiocyanate **3** afforded the corresponding monothiocarbamate **4a**. Cyclization of **4a** to 9-Boc-cyclobrassinon **5a** proceeded smoothly by triethylamine-mediated nucleophilic substitution of chloride, significantly facilitated by the activating effect of the Boc group. The Boc group can be removed thermally[20] or under acidic[21] or basic[22] conditions. We have found that deprotection of **5a** to **6a** can be effectively achieved by heating without solvent to 165–170°C, whereas treatment with acidic and basic reagents afforded decomposition products. The elaborated six-step procedure for the synthesis of cyclobrassinon (**6a**) can be successfully applied to the synthesis of its ethoxy-, methylamino- and 1-piperidinyl-analogues (**6b–6d**, Scheme 1). Employment of this synthetic sequence to the preparation of other 1,3-thiazino[6,5-*b*]indoles and the biological activity of synthesized compounds will be described elsewhere.

Experimental procedure for the preparation of cyclobrassinon: To a solution of **2** (0.55 g, 2 mmol) in dry tetrachloromethane (3 ml) was added a catalytic amount of AIBN and NBS (0.464 g, 2.6 mmol). The mixture was stirred at reflux for 10 min, cooled to 3°C, separated precipitate filtered off and the filtrate treated with a solution of KSCN (0.196 g, 2 mmol) in dry acetone (10 ml). After stirring for 15 min at room temperature and filtration with charcoal, the filtrate was evaporated and the residue was flash chromatographed on SiO_2 (10 g, benzene), to afford isothiocyanate **3** (0.277 g, 41%) as colourless crystals, mp 131–132°C (dichloromethane/hexane). A mixture of isothiocyanate **3** (0.277 g, 0.82 mmol) in methanol (11 ml) and acetone (11 ml) was stirred for 2 h at room temperature. Triethylamine (0.166 g, 0.23 ml, 1.64 mmol) was then added and stirring was continued for 1 h at room temperature. Then, 35 ml of water was added and the mixture was set aside for 1 h at 3°C. The separated precipitate was filtered off, washed with water and dried. Crystallization from dichloromethane/hexane gave 0.167 g (61%) of Boc-cyclobrassinon (**5a**) as colourless crystals, mp 212–214°C. Boc-cyclobrassinon (**5a**, 0.15 g, 0.45 mmol) was heated without solvent at 165–170°C for 40 min. Crystallization from methanol afforded 0.074 g (70%) of cyclobrassinon (**6a**) as colourless crystals, mp 221–223°C.

Spectral data for cyclobrassinon:[23] IR (KBr, cm^{-1}): 1567, 1627 (C=N–C=O). ^1H NMR (300 MHz, DMSO-d_6; δ, ppm): 4.18 (s, 3H, OCH_3); 7.39 (m, 2H, H-6, H-7); 7.66 (d, 1H, J = 7.5 Hz, H-8); 8.27 (d, 1H, J = 7.5 Hz, H-5); 12.69 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6; δ, ppm): 57.60 (CH_3); 102.24 (C); 111.92 (CH); 120.42 (CH); 122.01 (CH); 124.03 (CH); 124.29 (C); 136.88 (C); 137.52 (C); 165.50 and 165.66 (C=N–C=O). EIMS, [70 eV, m/z (%)]: 232 (M^+, 45), 175 (100), 146 (23), 120 (33).

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